REMARKS

The foregoing complete listing of the claims is provided for the convenience of the Patent Office. No amendment is made to the claims. Accordingly, no new matter has been added.

The claims under consideration are 11-14, 16, 20-27, 32-34, 36, 37, 44 and 50-66.

Withdrawal of the rejection under § 112, second paragraph is gratefully acknowledged.

The § 112, First Paragraph Rejection

The Specification stands objected to, and Claims 11-14, 16, 20-27, 32-34, 36, 37, 44 and 50-66 stand rejected, under 35 U.S.C. § 112, first paragraph, as allegedly lacking an enabling disclosure. Applicants respectfully traverse the objection and rejection as follows.

The focus of the enablement analysis in the Office Action is directed against the claim term "reference level of BAG-1 protein expression." The position stated in the Office Action appears to be that the person of skill in the art would not have been able to determine a reference level of BAG-1 protein expression. Applicants submit that the Office Action fails to provide adequate evidence or reasoning to support the contention that one of skill in the art would not have been able to determine a reference level of BAG-1. Applicants further submit that the evidence of record, including a publication by Turner et al. (Journal of Clinical Oncology, 19(4), 2001 (2001)) attached hereto as an Exhibit, provides adequate evidence that the person of skill in the art would have possessed the requisite skill to practice the claimed methods in view of the teaching provided by the instant Specification. Thus, the rejection under § 112, first paragraph should be withdrawn.

The Manual of Patent Examining Procedure states that the United States Patent Office (PTO) has the initial burden of establishing a reasonable basis for questioning the enablement provided for the claimed invention. M.P.E.P. § 2164.04. The question of adequacy of disclosure

in the context of § 112, first paragraph, is whether the person of skill in the art could have practiced the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 735, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The key word is "undue," not "experimentation," as the law permits a fairly large amount of experimentation so long as it is not "undue". *Id.* The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Id.* The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Id.*

Applicants submit that the instant Specification provides sufficient teaching for the person skilled in the art to determine the reference level of BAG-1. As stated in the Specification, the reference level may be determined by a plurality of methods. (Specification, page 17, lines 31-32.) The reference level may be determined by, for example, measuring the level of expression of BAG in non-tumorous cancer cells from the same tissue as the tissue of the cancer cells to be tested. (Specification, page 18, lines 5-6.) The reference level may also be a level of BAG expression of *in vitro* cultured cells which may or may not have been manipulated to simulate tumor cells, or may have been manipulated in any other manner which yields expression levels which accurately determine the reference level. (Specification, page 18, lines 5-13). The reference level may also be determined by comparison of BAG expression in populations of subjects having the same type of cancer. (Specification, page 18, lines 24-26.) This may be accomplished by histogram analysis. (Specification, page 18, lines 27-23.) The Office Action offers no evidence that the teaching of the Specification is unbelievable on its face,

nor that the person skilled in the art would have failed to understand the teaching of the Specification. Instead, the Office Action focuses on alleged defects in the references that Applicants cited to demonstrate the high level of skill in the applicable art.

According to the Office Action, there is no description or exemplification of an actual population of people who might provide samples from which the reference levels of BAG-1 could be obtained. This is incorrect. The Example set forth in the instant Specification illustrates at least one actual population from which a reference value may be obtained. (Specification, pages 32-36.) A retrospective correlative analysis was performed on BAG-1 and various other potential clinical outcome prognostic indicators. (*Id.*) Histostaining scores (H-scores) were obtained by determining the product of intensity and percentage. (*Id.*) To set cut-offs for dichotomization of data into groups having high and low levels of expression, the H-score data for the entire data set were displayed as dot-histograms with H-score on the x-axis and number of patient samples having a given H-score on the y-axis. (*Id.*) The H-score of 150 was used as a cut-off (reference level) for dichotomizing high versus low expression levels of BAG-1. (*Id.*) The Office Action gives no reason or evidence to support the notion that the illustrated methodology could not be analogously applied to tumor cells obtained from bodily fluids. Thus, the Office Action fails to provide adequate basis for a rejection under § 112, first paragraph, for lack of enablement.

The Office Action veers off-course in attempting to shift the focus off the PTO's burden of establishing non-enablement and onto supposed shortcomings of the references that Applicants have cited to demonstrate the high level of skill in the art. While Applicants have provided the Kim et al. reference to show the high level of skill in the art, the Office Action instead focuses on the alleged difficulty in choosing a reference level of c-erbB-2. Thus, the

Office Action misses the point made by Applicants, which is that statistical methods for setting reference levels of proteins are well-known in the art. Indeed, the Kim et al. reference actually shows a strong correlation between c-erbB-2 expression and surgical cancer stage. Thus, the Kim et al. reference validates Applicants' position that statistical methods of determining reference protein levels are routine in the art, notwithstanding the apparent lack of correlation between c-erbB-2 expression levels and some other indicia of tumor progression. Were this not the case, the Kim et al. reference could not have reasonably stated, as it does, that it seems likely that the determination of quantitative changes of oncogene products will prove to be of clinical use in classifying tumors into different prognostic categories, given that such changes at the molecular level may lead directly to alterations in tumor behavior. (Kim et al., page 96, column 1.) Thus, the Kim et al. reference provides evidence of the high level of skill in the art.

In further criticizing the Kim et al. reference, the Office Action states, without further elaboration, that the technique used in the Kim et al. reference would not be predictive of what should be used in practicing the claimed method. This criticism of Kim et al. misses the point of Applicants' citation of Kim et al., which is that statistical methods of determining reference protein levels are conventional in the art. Applicants do not dispute that c-erbB-2 is different from BAG-1, however the basic underlying statistical methodologies applied in Kim et al. are both applicable to practicing the claimed invention and conventional in the art. In fact, the authors of Kim et al. express no doubt that their chosen cut-off point of 100 fmol/mg cytosol protein is a valid. Although the Kim et al. reference does not show a correlation between c-erbB-2 expression levels and a various other clinical variables, the reference does demonstrate a strong correlation between c-erbB-2 expression and surgical stages. Thus, the Kim et al. reference demonstrates that statistical methods necessary to carry out the full scope of the

claimed invention are conventional and that they may be used to provide meaningful reference protein levels for studies of potential clinical markers. The Office Action does not provide an adequate rebuttal to this point.

The Office Action also poses the question of what population of patients should constitute a control population. Applicants respectfully submit that this question is more than adequately answered by the instant Specification, which teaches that a variety of controls may be used. For example, the degree of BAG-1 expression may be measured in a plurality of tumor cells from a number of subjects. The degree of BAG-1 expression may then be plotted against distribution to determine a suitable reference level of BAG-1 expression. This is precisely the methodology that is set forth in the Specification's Example. The Office Action gives no objective reason, and points to no evidence, that would cause the person of skill in the art to question the clear teaching of the instant Specification in general, and the Example in particular. Rather the Office Action propounds an unsubstantiated doubt, bolstered only by the lack of a working example employing bodily fluids, notwithstanding the closely analogous Example illustrating the method in solid tumors. Applicants submit that such unsubstantiated doubt cannot properly form the basis of a rejection under § 112, first paragraph, for lack of enablement.

The Office Action also criticizes Borre et al., which Applicants presented as further evidence of the high level of skill in the art with respect to statistical methods of determining reference protein levels. The Office Action does not appear to directly criticize the applicability of Boore et al., but instead shifts focus onto the H-scores cited in the instant Specification's Example. Thus, Applicants consider that the Office Action implicitly concedes the point raised by their citation of Borre et al., which is that statistical methods of determining reference protein levels are well-known to those skilled in the art.

The implicit thrust of the Office Action's H-score argument is that the person skilled in the art would not understand why Applicants selected an H-score of 150. Applicants point out that the Specification teaches use of a histogram, as discussed in more detail above. The Office Action fails to give any reason to believe that a person skilled in the art would not be able to interpret such a histogram following the instant Specification's clear teaching. Applicants further submit that the choice of H-score would be apparent to the person skilled in the art without undue experimentation. Indeed, this was Applicants' point in citing Borre et al., which demonstrates that it is conventional to choose, using well-known statistical methods, an appropriate H-score to represent the reference protein level. As evinced by Borre et al., the question of which H-score to choose as representing a reference level for a particular population is not one that would present untoward difficulty to the person having skill in this art.

In an effort to further illustrate the claimed methodology, Applicants present herewith as an Exhibit a publication by Turner et al., which describes in detail a study analogous to that set forth in the instant Specification's Example. In particular, Applicants point out Fig. 1 on page 994 of the Turner et al. reference, which depicts a BAG-1 histogram analogous to the one referred to in the instant Specification's Example. As can be seen from the Turner et al. BAG-1 histogram, a plot of percentage H-score (x-axis) against percentage of specimens (y-axis) results in a bimodal distribution with a local minimum at about 140 on the x-axis. The choice of an H-score of 150 is thus a logical choice, given this local minimum and the clear difference between the two modes in the histogram. Applicants submit that the Turner et al. reference illustrates how the person of skill in the art would employ entirely conventional statistical methods to determine the reference protein level (represented here by H-value) for a particular population. Thus, contrary to the Office Action, and in agreement with the instant Specification's Example,

the Turner et al. reference demonstrates that one skilled in the art would be able to choose a suitable reference protein level using the methods outlined in the instant Specification.

Applicants respectfully submit that, applying the reasonableness standard set forth in *In re Wands*, *supra*, the Office Action fails to establish that the one of skill in the art would have had to undertake unduly burdensome experimentation to practice the claimed invention. The Office Action fails to offer any firm foundation for its conclusion that the person of skill in the art would not have been able to practice the full scope of the claimed invention. Indeed, the weight of the evidence is in favor of enablement. Thus, Applicants request that the objection to the Specification and the rejection of claims 11-14, 16, 20-27, 32-34, 36, 37, 44 and 50-66 under 35 U.S.C. § 112, first paragraph, be withdrawn.

CONCLUSION

Applicant respectfully requests that the Examiner consider the remarks made above. Should the Examiner have any questions, he is invited to call the undersigned attorney. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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